REMARKS

Claims

Claims 2, 8, 10–17 are pending of which claims 2, 8, 10 and 13–17 are currently under examination pursuant to the restriction requirement mailed September 27, 2007.

Claims 11–12 are withdrawn from consideration pursuant to the aforementioned restriction/election requirement.

Claims 1, 3–7 and 9 were previously cancelled without prejudice or disclaimer.

Claim 18 is added by this paper.

Claim amendments

Dependent claim 16, in its amended form, complies with the statutory requirements under §112, ¶4 and is supported by the disclosure contained in, for example, paragraph [0018] of the published specification (US pub. No. 2005-0176633). Claim 18 is identical to amended claim 16, except that it is dependent on independent claim 17.

It is submitted that the amendments do not raise new matter. Entry thereof is earnestly solicited.

Rejections under §112, ¶1

Claims 2, 8, 10 and 13–17 are rejected under this section as allegedly lacking a written description of the manner of using the claimed antibody molecules for treating the disorders recited in the present claims and for allegedly being non-enabled. Applicants respectfully traverse these rejections.

Written Description

The basis for the rejection can be found in page 5 of the Office Action, wherein it is alleged that "the claims encompass functionalized antibodies, wherein antibodies are not only required to bind to pro-HB-EGF antigen but also yield a functional result, namely, that it inhibits activation of any growth factor receptor of the EGFR family...and is therapeutically effective against at least one cancer." This contention

is respectfully traversed.

Reconsideration of this rejection in view of the decision in *Martin v. Johnson*, 454 F.2d 746, 172 USPQ 391 (CCPA 1972) is respectfully requested. Therein the Court held that "the description need not be in *ipsis verbis* to be sufficient." Moreover, in *Ex parte Sorenson* 3 U.S.P.Q.2d 1462 (BPAI, 1987), it was held that the test for determining whether a claimed invention is adequately described in the specification is whether the originally filed disclosure reasonably conveys to a person having ordinary skill in the art that the applicant had possession of the subject matter later claimed. In *In re* Smythe, 480 F.2d 1376, 1384 (C.C.P.A. 1973), the court further held that it is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art to which the invention pertains would recognize from the disclosure that the Applicant's invention included those limitations. As such, controlling case law has routinely held that contrary to the PTO's contentions, *ipsis verbis* support for the claimed subject matter is not required insofar as the originally-filed disclosure *reasonably* conveys to an ordinary skilled worker that the Applicant was in possession of the claimed subject matter.

Contrary to the PTO's contention, Applicants submit that the originally-filed specification provides more than sufficient disclosure to guide one of ordinary skill in the art to practice the claimed invention in its broadest possible scope. To this end, paragraphs bridging [0007]-[0010] of the published specification (US pub. No. 2005-0176633) expressly teaches that "it was found that inhibition of growth-factor receptor activation caused by increased G-protein mediated signal transduction leads to an inhibition of cancer progression, particularly cell migration and invasivity, as well as to an inhibition of anti-apoptosis...the growth-factor receptor is preferably EGFR or another member of the EGFR family, such as HER-2, HER-3 or HER-4." At paragraph [0006] the specification teaches that "a subject matter of the present invention is the use of a compound which is capable of inhibiting activation of a growth-factor receptor of the EGFR family...for the prevention or treatment of processes selected from cell proliferation, cell migration, invasivity and anti-apoptosis in a disorder, which is associated with increased G-protein mediated signal transduction." Paragraph [0014] of the published specification discloses disorders that

may be treated, for example, cancers of the colon, kidney, liver, bladder, pancreas, prostate, gastro-intestines, breast, lung, thyroid, pituitary, adrenal, ovary or glioblastoma. The specification proceeds to teach that the "compound may act on a growth-factor receptor ligand precursor, which is preferably a membrane-associated molecule. In a particularly preferred embodiment the growth-factor ligand precursor is pro-HB-EGF which is cleaved to HB-EGF by a protease." With respect to compounds having the aforementioned properties, the specification expressly teaches that an example of a compound "which acts on a growth-factor receptor ligand precursor is an antibody which is capable of binding to pro-HB-EGF and which thereby blocks its processing." See paragraph [0010] of the published specification. As such, contrary to the Examiner's contentions, the disclosure in the specification literally discloses antibodies having the claimed properties.

Reduction to practice

At page 6 of the Office Action, the Examiner alleges that "Applicants have yet to site [sic] a single example of an antibody **actually having been reduced to practice** and for which antibody meeting all of the requirements of the instant claims (emphasis added)." This requirement is legally misplaced. For example, MPEP §2163 states that "possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, **or** by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." In view of the foregoing analysis, the present specification teaches to one skilled in the art that antibodies that bind to pro-HB-EGF may be used to block the processing of the ligand and inhibit the concomitant activation of EGFR, and such antibody molecules may be therapeutically utilized in the treatment of cancers. It should be further noted that HB-EGF antibodies were known in the art before the instant application was filed. For example, Marikovsky et al. (PNAS, 1993), which was published before Applicants' earliest priority date (March 8, 2002), describes polyclonal anti-sera against HB-EGF. A copy of this article is enclosed herewith for the

Examiner's review. Purified antibodies against HB-EGF are similarly described in literature – a PUBMED search with the term "HB-EGF antibody" reveals several articles that were published before Applicants' earliest priority date. To this end, it should be further noted that antibodies against HB-EGF are commercially available via Santa-Cruz Biotechnology (Santa Cruz, CA, USA). See the enclosed catalog information from the vendor, which is enclosed herewith as Exhibit A.

As to antibodies that bind to pro-HB-EGF, methods for obtaining such, for example, via immunizing rabbits, hamsters, or the like, were known in the art. The product information from Santa-Cruz Biotechnology provides a disclosure of the antigenic determinants in HB-EGF that were used to raise antibodies against HB-EGF. Conventional screening methods could be reliably used to identify antibodies which bind to the precursor molecule and block processing thereof. As an example, *in vitro* processing of pro-HB-EGF in the presence and absence of a blocking antibody could be studied by assaying for HB-EGF fragments in the cell-culture milieu with conventional analytical instruments (e.g., HPLC).

Evidentiary documents

The disclosure(s) in Molina et al. (Cancer Research, 2001) and the product information on trastuzumab were furnished to the PTO to demonstrate that the field of immuno-therapeutics has matured to a point that antibodies that are potentially useful in the *in vitro* setting can be improved and further screened for clinical utilization. The Office Action now contends that "arguments of counsel *alone* are not found to be sufficient in overcoming the rejection." This allegation is without merit. First, the disclosure in the specification conveys to one skilled in the art that Applicants had possession of the claimed invention. The representative examples in the specification, further in view of the experimental evidence provided in the Huber declaration, reasonably convey to a skilled worker that antibodies that bind to and block the processing of pro-HB-EGF not only inhibit EGFR transactivation but also disrupt the down-stream signaling events and their concomitant effect on predisposition to cancer cell phenotype. The descriptive portion of the specification further teaches that many cancers are characterized by over-expression and/or

increased activation of the EGFR. As such, the potential therapeutic utility of antibodies that bind to pro-HB-EGF and block cellular signaling initiated thereby is clearly credible, as required. Favorable reconsideration is respectfully requested.

It is therefore respectfully submitted that the originally-filed specification conveys to the skilled worker that antibodies that bind to pro-HB-EGF are useful in treating cancer. Withdrawal of the rejection is respectfully requested.

Enablement

With respect to the enablement rejection, the Examiner's contentions are as follows:

The Examiner contends that the evidence in the declaration is insufficient to overcome the enablement rejection allegedly because

(a) the data in the declaration does not demonstrate a correlation between GPCR-induced phosphorylation of EGFR and HB-EGF and cancer-associated proliferation, migration, invasivity and anti-apoptosis.

(b) the data in the declaration does not demonstrate a relationship between inhibiting LAP or thrombin-induced EGFR phosphorylation *in vitro* in COS-7 cells and the utility of the same antibody in treating any cancer cell phenotype (i.e., proliferation, migration, invasivitiy, and anti-apoptosis).

(c) the data in the declaration does not demonstrate a correlation between blocking pro-HB-EGF processing would affect the aforementioned cancer cell pheonotype in colon cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, lung cancer, or ovarian cancer.

(d) the data in the declaration does not demonstrate a correlation between inhibiting phosphorylation of the EGFR substrate and inhibiting any GPCR-mediated activation of the EGFR family of proteins such as Her-2, Her-3, and Her-4.

(e) the data in the declaration demonstrate the inhibitory effect of antibodies against HB-EGF and not pro-HB-EGF.

With regard to the PTO's contention in (e), Applicants point to the disclosure in

paragraph [0009] of the published specification, wherein it is expressly taught that "growth-factor ligand precursor pro-HB-EGF is cleaved to HB-EGF by a protease [and that the inhibitor] is an antibody, which is capable of binding to pro-HB-EGF and which thereby blocks its processing." It would be reasonable to assume that an antibody which binds to HB-EGF (as shown by the declaration) would also bind to its precursor molecule, pro-HB-EGF. See also *supra*, with respect to the written description rejection.

With respect to point (c), Applicants submit that insofar as the downstream effects of EGFR phosphorylation were known in the art explicit demonstration of the after-effects of inhibition of this initiation event is not necessary at all. To this end, the disclosure in the specification teaches to one skilled in the art that GPCR ligands which initiate tyrosine phosphorylation of EGFR and Shc concomitantly result in downstream phosphorylation of mitogen activated protein kinase (MAPK), cell proliferation, anti-apoptotic phenotype, increased cell migration and increased cell invasion. See, Figs. 1-7. The specification further exemplifies that compounds such as BB94 and AG1478 not only inhibit the initiating EGFR phosphorylation and transactivation events, but also prevent the phenotypic changes associated therewith. As such, contrary to the Examiner's assertion, the totality of Applicants' disclosure not only demonstrates a correlation between EGFR transactivation and tumorigenesis but also establishes that compounds which block processing of pro-HB-EGF inhibit the down-stream signaling events and the cancer phenotypes resulting therefreom. In contrast, the references cited by the Examiner, e.g., Fujimori (*Journal of Nuclear Medicine*, 1990), Beckman (*Cancer*, 2007), Thurber (*Advanced Drug Delivery Review*, 2008) and Rudnick (*Cancer Biotherapy and Radiopharmaceuticals*, 2009), do not call into question the objective statements of enablement provided by Applicants' disclosure.

With respect to point (c), Applicants submit that the experiments with COS-7 cells (kidney cancer cells from *Cercopithecus aethiops*, i.e., grivet) unequivocally demonstrate that the antibodies of the instant invention are, at a minimum, effective against kidney cancer.

With respect to point (b), Applicants' specification teaches that LPA or

thrombin-induced EGFR phosphorylation *in vitro* has a **direct, measurable** effect on the predisposition to cancer phenotype. To this end, Fig. 3 shows that LPA-induces proliferation of lung cancer cell line H292. The data in Fig. 4 show that LPA-induces anti-apoptotic effects in the bladder cancer cell line TccSup. Fig. 5 shows that LPA-induces migration in the kidney cancer cell line A498. Fig. 6 contains data from a study on LPA-induced wound closure in the kidney carcinoma cell line ACHN. Fig. 7 shows that LPA-induces invasion in the kidney carcinoma cells. The specification further provides compelling evidence to support Applicants' position that the initiating event for the aforementioned cancer phenotypes is activation of the EGFR pathway via tyrosine phosphorylation. See, the data in Figs. 1 and 2. Accordingly, contrary to the Examiner's assertion, the disclosure in the specification along with the data in declaration does demonstrate a relationship between LPA or thrombin-induced *in vitro* EGFR phosphorylation in cancer cells and the utility of the claimed inhibitory compounds in reversing the cancer cell phenotype resulting from EGFR transactivation (i.e., proliferation, migration, invasivitiy, and anti-apoptosis).

With respect to the Examiner's contention in (a), Applicants submit that RTK-phosphorylation assay is a standard technique for determining the effects of tyrosine phosphorylation on cell proliferation. Such has been exemplified by Applicants original disclosure, for example, the evidence presented in Figs. 1-7. The data in the declaration clearly demonstrates that antibodies against HB-EGF are suitable for treating hyperproliferative diseases, i.e., diseases associated with cell proliferation, and in particular diseases that are associated with an abnormal GPCR-induced receptor tyrosine kinase signal. Anti-HB-EGF-induced inhibition of cancer cell phenotypes is further described in the co-owned post-published European patent application EP 08 802 677.8 (published as WO 09/040134). A copy of this publication is enclosed herewith for the Examiner's review.

Other general contentions of non-enablement

Demonstration of *in vivo* efficacy

The Office Action alleges that results of *in vivo* efficacy of the antibody are required to satisfy the enablement provisions under §112, ¶1. Contrary to the

PTO's contention, demonstration of *in vivo* clinical data is not required at all. Moreover, decades of scientific studies, both at the basic and clinical levels, have established that *in vitro* studies "reasonably correlate" with their *in vivo* counterparts. As outlined *supra*, the specification provides more than what is required under the statute. There is no basis for the general allegation that clinical correlations are generally lacking for *in vitro* assays and/or cell-culture based assays. Furthermore, the patent law is in accord with the realities of pharmaceutical arts and controlling case law supports Applicants' position. See, for example, *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), *Fujikawa v. Watanasin*, 39 USPQ.2d 1895 (1996) and the guidelines under MPEP §2164.02. Applicants' disclosure provides adequate guidance to objectively enable one of ordinary skill in the art to test the therapeutic activity of the claimed antibody molecules, and to use the same in the practice of the presently claimed methods without undue experimentation. Favorable reconsideration is respectfully requested.

Working examples

The Office Action further alleges that absent working examples providing evidence, the instantly claimed methods are non-enabled. Working examples are not required to establish enablement. As stated by the court *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

The assertion of undue experimentation in the rejection is conclusory, and fails to address the fact that method claims are directed to a manner of using specific compounds. Further, as discussed above, the specification provides more than sufficient guidance to determine the efficacy of anti-pro-HB-EGF antibodies, so that the claimed methods can be practiced using no more than routine experimentation. Finally, a high level of skill does not establish that one skilled in the art would have reasons to doubt the veracity of the statements in Applicants' specification with respect to the utilization of antibody molecules in immunotherapy.

As such, it is respectfully submitted that within the current state of the art at the time of filing there is no basis for a rejection for lack of enablement in a case where Applicants provide more than sufficient guidance as to how the molecules can be made and their activity tested. Withdrawal of the rejection is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Encl.

(a) Exhibit A
(b) Markovsky et al.
(c) WO 09/040134